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(54) Drug-containing tape preparations

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## SPECIFICATION

**1. Title of the Invention**

Drug-containing tape preparations

**2. Scope of the Patent Claims**

1) A drug-containing tape preparation characterized in that it comprises a moulded mixture in which a compound where a drug has been clathrated in a clathrating agent is compounded in a polymeric material and in which the said clathrating agent is compounded in such a way as to account for not more than 90 wt.% of the said mixture.

2) A drug-containing tape preparation, according to claim 1, in which the drug is a coronary blood vessel dilator which has a nitrous acid ester in the molecule.

3) A drug-containing tape preparation, according to claim 2, in which the coronary blood vessel dilator is nitroglycerine.

4) A drug-containing tape preparation, according to claim 1, in which the clathrating agent is cyclodextrin.

5) A drug-containing tape preparation, according to claim 1, in which the polymeric material is a sticky material which has pressure sensitive adhesive properties.

6) A drug-containing tape preparation, according to Claim 1, in which the clathrating agent content in the moulded mixture is from 3 to 50 wt.%.

7) A drug-containing tape preparation, according to any of claims 1 to 6, in which a film-like support material is fixed to the surface of and/or incorporated within the said preparation.

**3. Detailed Description of the Invention**

The invention concerns drug-containing tape preparations which contain a compound where a drug has been clathrated in a clathrating agent.

More precisely, the invention provides drug-containing tape preparations which are intended to administer continuously and transdermally a coronary blood vess l dilator such as nitroglycerine or an antiphlogistic analgesic such as indomethacin through a pre-determined site on the skin into the circulatory syst m.

Compounds which have a nitrous acid ester within the molecul such as nitroglycerine and isosorbide dinitrate for example are known as anti-angina pectoris drugs which have an excellent coronary blood vessel dilating effect.

Drugs comprising these compounds are widely used for the treatment of angina pectoris attacks in the form of under-the-tongue tablets and their excellent effect has long been recognised, but on the other hand the effect persists for only a short period of time and there are problems with accompanying side effects such as headache and nausea when the concentration in the blood reaches its peak. Furthermore, there is another problem in that nitroglycerine is very volatile so that the nitroglycerine content of an under-the-tongue tablet falls with the passage of time and it does not have the expected efficacy when it is finally used.

Nitroglycerine soft ointments have been developed as a means of resolving these problems and these can be used not only for treatment but also for preventing the onset of angina pectoris attacks, and in this case the persistence of the effect is greater than that with the under-the-tongue tablets, but the rate of supply of the drug cannot be controlled and the situation is such that the problem with side effects is still unresolved. Soft ointments are stored in a closed system and so there is little vaporisation of the nitroglycerine, but dispersal into the air occurs more rapidly than take-up through the skin after it has been applied to the body surface and so a complicated procedure in which the site of application is sealed with a plastic film, for example, is required.

Furthermore, the admixture of nitroglycerine in the adhesive layer which is formed on a tape support as in the case of a normal sticky tape for therapeutic purposes has been considered, but the nitroglycerine may permeate through the tape support to the tape surface and be lost by vaporisation and there is problem in that satisfactory efficacy will not be obtained in use.

As a result of thorough research carried out on the basis of an understanding of the situation with prior art as outlined above with a view to providing a drug-containing tape preparation with which all of the various conditions such as prolonging the persistence of the effect, controlling the rate at which the drug is supplied, ensuring that most of the drug is absorbed through the skin and not lost by vaporisation in us or with the passage of time and ensuring

ready up-take without the need for any complicat d procedure can be satisfied, the inventors have discovered that a tape preparation which satisfies the above mentioned conditions can be obtained by clathrating the drug with a clathrating agent and compounding the clathrated drug in a polymeric material in such a way that the clathrating agent content is less than a fixed amount, and the invention is based upon this discovery.

That is to say, the invention provides a drug-containing tape preparation, characterized in that it comprises a moulded mixture in which a compound where a drug has been clathrated in a clathrating agent is compounded in a polymeric material, and the said clathrating agent is compounded in such a way as to account for not more than 90 wt.% of the said mixture.

One embodiment of the invention is a tape, sheet or leaf-type preparation for which a mixture of a compound where a drug has been clathrated in a clathrating agent (referred to hereinafter as a clathrate compound) and a polymeric material have been moulded. With this preparation the clathrating agent is softened and dissolved by the moisture which is supplied from the body when the preparation is fitted closely on the surface of the body and the drug which is released from the clathrate diffuses and migrates toward the surface of the body and the body is able to take-up the drug continuously.

Another embodiment of the invention is a preparation where a coated film comprising a clathrate compound and an ordinary adhesive which has pressure sensitive adhesion properties is formed on a film-like support material. This type of preparation can be stuck directly onto the surface of the body for use.

The fact that the drug-containing tape preparations of this invention act in such a way as to satisfy the various conditions referred to above by the ingenious use of the properties, function and material of the clathrating agent which is used to prepare the clathrate compound will become clear from the following description.

For example, a drug-containing tape preparation of this invention is not subject to loss of the drug due to vaporisation under normal circumstances and it is constructed in such a way that the clathrate with the clathrating agent is broken down on supplying a considerable amount of moisture and the drug is rel ased.

Hence, when the tape preparation is in intimate contact with the body surface and moisture is supplied from the body surface most of the drug is released towards the body surface and so the drug is supplied to the body surface without wastage.

The cyclodextrins comprising cyclic oligosaccharide homologues known as Shardinger dextrin and cyclodextrin are used as clathrating agents which exhibit such a function. Typical cyclodextrins include α-cyclodextrin where six D-glucose units are α-1,4- bonded in the form of a ring, and β-cyclodextrin where seven D-glucose units are α-1,4- bonded in the form of a ring. Other clathrating agents include γ-cyclodextrin and crown ethers.

The drug which is clathrated in these clathrating agents may be, for example, a coronary blood vessel dilator where a nitrous acid ester is included within the molecule, such as nitroglycerine, isosorbide dinitrate erythritose tetranitrate, pentaerythritose tetranitrate and mannitol hexanitrate, or an antiphlogistic analgesic such as indomethacin.

There are various methods for clathrating the drug in the clathrating agent and the two methods indicated below are useful.

(1) Water in an amount of from 8 to 50 times by weight is added to a suitable amount of cyclodextrin and the mixture is heated to from 30 to 90°C to prepare an aqueous solution in which all of the cyclodextrin has been dissolved. A liquid drug can then be added to this aqueous solution as it is or a powder-like drug can be formed into a liquid by dissolution in a solvent such as methanol, ethanol, acetone or ether and added to the aqueous solution, the addition being made gradually and with stirring, and the mixture is left to cool after being stirred for from 2 to 10 hours and the solid which precipitates out is recovered by filtration and dried, and a powder-like clathrate compound is obtained.

(2) Water in an amount of from 2 to 5 times by weight is added to a suitable amount of cyclodextrin to form a paste and the drug which has been dissolved in a small amount of solvent is added to this paste and mixed for from 2 to 6 hours and then it is washed with a suitable solvent and dried and a powder-like clathrate compound is obtained.

A powder-like clathrate compound obtained using such a method is compounded with a polymeric material to form a mixture. Th mixture obtain d,

depending on the nature of th polymeric material, can be used to form a drug-containing tape preparation in which the mixture itself has the prescribed form or a drug-containing tape preparation where the mixture is applied to an auxiliary film-like supporting material and maintained with the prescribed form.

The mixture is softened by the drug and, with either of these types of tape preparation, the clathrating agent from which the clathrate compound is formed has the function of preventing effectively deformation of the tape preparation and leaving part on the surface of the body by replenishment by dispersion and by means of its viscosity increasing action.

The group of materials which do not have pressure sensitive adhesive properties in the normal state in which the clathrate compound can be maintained in a dispersed state are one group of the aforementioned polymeric materials, and this group includes soft poly(vinyl chloride), soft polyamide, polyolefins, poly(vinyl alcohol), polyacrylic resins, heat curable and room temperature curable type silicone rubbers, and ethylene-vinyl acetate copolymers. Tape preparations in which these materials are used can be made by simply moulding the mixture of clathrate compound and said material, and the tape preparations obtained have satisfactory moisture permeability when compared with the aforementioned polymeric materials alone as a result of the action of the clathrating agent and they have a construction such that little of the drug which is contained is left behind in the tape preparation.

Another group of polymeric materials comprises polymeric materials which have pressure sensitive adhesive properties in the normal state and in which the clathrate compound is maintained in a dispersed state and which have a suitable amount of moisture permeability, and examples of some of the materials in this group include acrylic compositions comprising copolymers of (meth)acrylic acid esters such as n-butyl (meth)acrylate, hexyl (meth)acrylate, 2-ethylbutyl (met)acrylate, iso-octyl (meth)acrylate, 2-ethylhexyl (meth)acrylate, and tridecyl (meth)acrylate, with functional monomers such as (meth)acrylic acid, itaconic acid, maleic acid, maleic anhydride, hydroxyethyl acrylate, hydroxypropyl acrylat , acrylamide, dimethylacrylamide, methylaminoethyl methacrylat and

methoxyethyl (meth)acrylate which are copolymerizable with these est rs, and/or vinyl monomers such as acrylonitrile, vinyl acetate and vinyl propionate.

Other examples include rubber-based adhesives which have a rubber, for example silicone rubber, polyisoprene rubber, polyisobutylene rubber, styrene-butadiene-(or isoprene)-styrene block copolymer rubber, acrylic rubber or natural rubber, as the main component, and vinyl based adhesives which have vinyl-based polymers such as poly(vinyl ether), poly(vinyl alcohol) and poly(vinyl acetate) as the main component.

With the tape preparations in which such sticky materials have been used as a supporting medium for the clathrate compound, in those cases where a sticky material which provides better characteristics as a result of the addition of a crosslinking component in the process in which the said sticky material is being produced is used, the clathrating agent from which the clathrate compounds is formed stabilises the drug, which is to say that it effectively prevents the drug from reacting with any of the materials from which the sticky material is composed and causing modification.

In this way the clathrating agent from which the clathrate compound is produced not only functions in such a way as to prevent dispersal of the drug in the normal state but also has many other effects such as ensuring that the drug is supplied precisely to the body surface without waste as indicated earlier, preventing softening of the polymeric material which is the supporting medium by the drug and stabilising the drug, but these effects are only obtained by adjusting the amount of clathrating agent which is included in the mixture of clathrate compound and polymeric material to not exceeding 90 wt.% at the most.

Even if the amount of clathrating agent does exceed 90 wt.% this does not limit the control of the amount of drug which is being supplied, the prevention of softening or the stabilisation of the drug, but on the other hand it reduces the physical strength of the moulded mixture and reduces the pressure sensitive adhesion properties of the adhesive and also has an adverse effect on the uniformity f the dispersion in the polymeric material and so this is undesirabl , and in fact the clathrating agent content is preferably not more than 70 wt.% and

more desirably from 3 to 50 wt.%, and in practice it is preferably from 5 to 30 wt.%.

Suitable amounts of auxiliary agents which have the function of promoting the breakdown of the clathrate and drug release and of promoting the up-take of the drug by the skin, such as propylene glycol, diethylene glycol, diisopropyl glycol, ethyl laurate, dimethylacetamide and diethyl sebacate can be added to the clathrate compound and polymeric material mixture.

Mixtures comprising clathrate compound and polymeric material and any auxiliary agents which are added as required of this type can be formed into a tape preparation by being moulded as the mixture alone into the prescribed tape, sheet or leaf-like form, or they may be formed into a tape preparation by forming a layer of the mixture on one side or both sides of a film-like support comprising nonwoven fabric, woven fabric, knitted fabric, leather, foam-based film, metal foil or a plastic film or sheet in the form of a layer of mixture using a means such as coating or pasting for example.

The abovementioned film support material is selected or processed in such a way that sufficient moisture is supplied to the tape preparation from the skin and so that there is rash formation due to irritation of the skin, and the composite system of film support material and mixture layer is preferably devised in such a way that it has a moisture permeability of from 150 to 1900 $g/m^2/24$ hr.

The thickness of the tape preparation is of no great importance but it is generally from 30 to 500 μ, and the thickness or the amount of clathrate compound added to the polymeric material is preferably adjusted in such a way that the drug content per unit area is from 50 to 2000 $\mu g/cm^2$.

A drug-containing tape preparation of this invention which has been constructed in this way loses hardly any of the drug by vaporisation in the normal state and supplies most of the drug to the surface of the body when used and so the drug can be supplied precisely and it is possible to maintain a blood concentration of from 2 to 15 ng/ml serum for a period of from 6 to 24 hours. Moreover, because it is a tape-typ preparation it is very conveni ntly used by simply sticking the tape directly or with s me oth r auxiliary me ns on the surface of th skin.

Even when they ar stored for prolonged periods of time the drug-containing tape preparations of this invention are stable and the fact that they supply the drug without wastage to the circulatory system continuously via the skin through the predetermined site is confirmed by means of the illustrative examples below. In this specification the term "parts" signifies "parts by weight".

**Example 1**

Clathrate Compound

β-Cyclodextrin (40 g) and 700 ml of water were heated to 70°C and the cyclodextrin was dissolved completely to form a solution and then a solution obtained by dissolving 6 g of nitroglycerine in 12 ml of acetone was slowly added in a dropwise manner. After the drip feed had been completed the mixture was stirred for a further period of 1 hour and then left to cool for about 4 hours, whereupon a white clathrate compound precipitated out. This was recovered by filtration and dried, and 35 g of a powder-like clathrate compound which had nitroglycerine content of 12.3 wt.% were obtained.

Drug-containing Tape Preparation

An ethylene-vinyl acetate copolymer (75 parts) which had a vinyl acetate content of 28 wt.% was dissolved in chloroform and 25 parts of the above mentioned clathrate compound were added and the mixture was cast on a mould-release liner in such a way as to provide a thickness after drying of 80 μ and dried for 15 minutes at 80°C, and a drug-containing tape preparation of nitroglycerine content 190 $\mu g/cm^2$ was obtained.

**Example 2**

| | |
|---|---|
| Iso-octyl acrylate | 75 parts |
| Methoxyethyl acrylate | 20 parts |
| Methacrylic acid | 5 parts |
| Benzoyl peroxide (BPO) | 0.2 part |
| Ethyl acetate | 25 parts |

The compounds indicated above were introduced into a four-necked flask and heated to a temperature of from 65 to 68°C under an inert gas atmosphere and stirred and reacted for 10 hours, controlling th reaction time, while adding 125 parts of ethyl acetat in a dropwise manner, and then the mixture was

matured for 2 hours with heating at from 75 to 80°C and a copolymer solution with a 40% solution viscosity of 470 poise was obtained with a polymerization rate of 99.5%.

The said solution was diluted with ethyl acetate to form a 25% base and 320 parts of the diluted material were mixed with 20 parts of the clathrate compound used in Example 1 and dispersed.

The liquid mixture prepared in this way was coated in such a way as to provide a thickness after drying of 60 μ on the surface of a polyethylene film and dried for 5 minutes at 80°C and a drug-containing tape preparation of nitroglycerine content 150 $\mu g/cm^2$ was obtained.

**Example 3**

| | |
|---|---|
| 2-Ethylhexyl acrylate | 65 parts |
| Vinyl acetate | 33 parts |
| 2-Hydroxyethyl acrylate | 2 parts |
| Azobisisobutyronitrile | 0.2 part |

The compounds indicated above were processed in the same way as in Example 2 and a copolymer solution of 40% solution viscosity 780 poise was obtained with a polymerization rate of 93%.

The said solution was diluted with ethyl acetate to form a 25% base and 340 parts of the diluted material were mixed with 15 parts of the clathrate compound used in Example 1 and dispersed.

The liquid mixture prepared in this way was used in the same procedure as in Example 2 and a drug-containing tape preparation of nitroglycerine content 110 $\mu g/cm^2$ was obtained.

**Example 4**

| | |
|---|---|
| Iso-octyl acrylate | 77 parts |
| Hexyl acrylate | 20 parts |
| Acrylic acid | 3 parts |
| Nonylphenylpolyethylene glycol | 5 parts |

Th compounds indicated above were introduced into a four-n ck d flask and then, after stirring th mixture, 200 parts of ion xchang d water were added and the mixture was stirred and th internal temperature was raised to 60°C

under an inert gas atmosph r and a polymerization r action was carried out for 3 hours using 0.2 part with respect to the compounds of ammonium persulphate. The mixture was then matured for 2 hours at from 80 to 85°C and a copolymer of viscosity (4 rpm) 38 poise was obtained with a polymerization rate of 99.8%.

The clathrate compound used in Example 1 (20 parts) was mixed with 240 parts of the said copolymer liquid and thoroughly dispersed. The mixture was then coated so as to provide a thickness after drying of 60 μ on a polyethylene film and dried for 10 minutes at 80°C and a drug-containing tape preparation of nitroglycerine content 150 μg/cm$^2$ was obtained.

**Comparative Examples 1 to 3**

Nitroglycerine was added to the copolymer solution (25% base) or liquid of Examples 2 to 4 and drug-containing tape preparations which had the same nitroglycerine contents as in each of the examples were then obtained.

The test results obtained with Examples 1 to 4 and Comparative Examples 1 to 3 are shown in Table 1.

**Table 1**

| | | Example | | | | Comparative Example | | |
|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 1 | 2 | 3 |
| Initially determined value (μg/cm$^2$) | | 190 | 150 | 110 | 150 | 140 | 101 | 133 |
| Determined value after 1 month at 80°C (μg/cm$^2$) | | 180 | 145 | 105 | 145 | 106 | 72 | 99 |
| Blood Concentration (ng/ml) | 3 hours | 7.4 | 5.1 | 6.4 | 5.0 | 3.9 | 2.5 | 6.0 |
| | 10 hours | 6.2 | 4.3 | 7.8 | 5.4 | 1.0 | 1.5 | 2.5 |
| | 24 hours | 4.5 | 4.0 | 3.3 | 4.1 | 0.5 | 0.3 | 1.0 |
| | 48 hours | 2.0 | 1.0 | 0.5 | 0.5 | - | - | - |

Method of Determining Blood Concentration

Blood was sampled and centrifuged immediately and 8 ng of isosorbide dinitrate were added to 2 ml of the plasma obtained as an internal standard (10 μl of a 0.8 μg/ml n-hexane solution of isosorbide dinitrate in n-hexane were added) and the mixture was shaken for a f w seconds. Then 5.5 ml of n-h ptane w re added and the mixture was shaken for 40 s conds. Immediately after shaking the

organic solvent layer was transferred to a Spitz tube and the solvent was distilled off with a washed inert gas. Then 100 μl of n-hexane were added to and shaken with the residue and the sample obtained was eluted by means of a gas chromatograph furnished with an electron capture type detector.

The set conditions on the electron capture type detector fitted gas chromatograph were as follows:

Radiation Source: 10 mCi $^{63}Ni$

Carrier Gas: Nitrogen gas, 20 ml/min (flow rate)

Column Temperature: 130°C

Injection Temperature: 165°C

Detector Temperature: 180°C

Column: Glass column (silane treated) of internal diameter 2.4 mm and length 1.2 m.

Packing Material: 3% Silicone OV-101 (80 - 100 mesh)

As is clear from the illustrative examples described above, drug-containing tape preparations where nitroglycerine as a drug which has been clathrated using cyclodextrin as a clathrating agent has been compounded with a polymeric material show little loss of the drug by dispersal and a remarkably long persistence time.

**Translator's Note**

The figures in Table 1 were extremely hard to read and should be checked against a better copy.